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DNA-based asymmetric organometallic catalysis in water†

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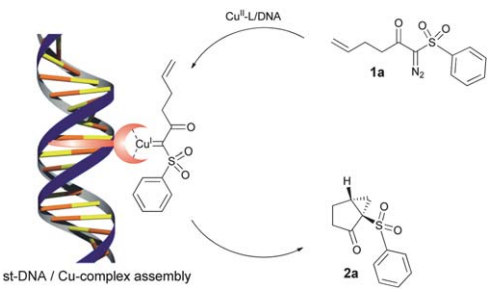
Here, the first examples of DNA-based organometallic catalysis in water that give rise to high enantioselectivities are described. Copper complexes of strongly intercalating ligands were found to enable the asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfones in water. Up to 84% ee was achieved, in the presence of salmon testes DNA as the only source of chirality, using dipyrido [3,2-*a*:2′,3′-*c*]phenazine (dppz) derivatives as ligands.

Introduction

DNA-based asymmetric catalysis has emerged as a powerful new approach to asymmetric catalysis in water.[1–6] In this concept, a hybrid catalyst is created by binding a catalytically active metal complex to a DNA scaffold, which allows the unique chirality of DNA to be translated into enantioselectivity in the catalyzed reaction. This concept has been applied successfully in a variety of catalytic enantioselective reactions such as Diels–Alder,[7,8] Friedel–Crafts,[9,10] (oxa-)Michael reactions,[11,12] fluorinations[13] and the *syn*-hydration of enones,[14] with good to excellent ee values in all cases. These reactions have in common that they are all Lewis acid catalyzed, employing Cu^{II} as the catalytic metal ion. The same Diels–Alder and Friedel–Crafts reactions were also used in a related approach involving combinations of DNA G quadruplexes and metal salts.[15,16] Indeed, examples not involving Lewis acid catalysis are scarce and, to date, have not resulted in high enantioselectivities. An allylic amination reaction catalyzed by an Ir^{III} coordinated to a chiral diene ligand that was covalently anchored to DNA, was reported by Jäschke *et al.*[17] It was shown that the nature of the oligonucleotide modulates the stereochemical course of the reaction, *i.e.* which enantiomer is obtained in excess. However, the maximum ee values achieved were low and similar to those obtained with the Ir^{III} complex of the chiral diene ligand alone. Thus, no beneficial effect of the DNA scaffold was observed. In another example, Pd-complexes of phosphine modified mono-nucleotides were also used in allylic substitution reactions with good ee values in THF as solvent. But only low activities and enantioselectivities were obtained with longer oligonucleotides in water.[18] In view of the enormous synthetic potential, we aim to expand the catalytic scope of DNA-based asymmetric catalysis to include organometallic reactions. Here, we report the first example of DNA-based organometallic catalysis in water that results in high ee values: the catalytic enantioselective intramolecular cyclopropanation of α-diazo-β-keto sulfones.

Carbenes are important intermediates in organic synthesis[19] and the catalytic formation of organometallic carbenoids in the presence of transition metals makes them reliable and controllable species for asymmetric catalysis.[20–23] Cyclopropanations are well known reactions of carbenes and especially rhodium[24] and copper[21,22] complexes are recognized as preferred catalysts in organic solvents. However, due to the low solubilities of transition metal catalysts in water and the high tendency for insertion into the O–H bond of water, it still remains a major challenge to perform asymmetric cyclopropanation in aqueous media.[25,26] Relatively few examples of metal catalysts that give rise to high stereo- and/or enantioselectivities in water or aqueous media have been reported and these are based on rhodium[27–30] and ruthenium[31–33] and more recently cobalt[34,35] and iron.[36,37]

Nakada *et al.* published the intramolecular cyclopropanation of **1a** under strictly anhydrous conditions in toluene catalyzed by CuOTf/bisoxazoline complexes.[38] The diazo-compound **1a** is stable at room temperature for several months, but readily



Scheme 1 Intramolecular cyclopropanation of **1a** in water using a DNA-based catalyst.

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forms a metal carbene complex with Cu^{I} at room temperature, which subsequently reacts in an intramolecular cyclopropanation to give **2a**. This transformation was used as the benchmark reaction in the present study. Due to the large structural change occurring during an intramolecular cyclopropanation, we expected this reaction to be sensitive to the chirality of DNA when taking place in close proximity to the DNA double helix (Scheme 1).

Results and discussion

The catalytic reactions were performed in 10 mM 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer pH 6.5 at room temperature. For formation of the copper-carbenoid with **1a**, the catalyst needs to be in the Cu^{I} oxidation state. However, the use of Cu^{I} complexes under these conditions resulted in partial precipitation of the catalyst. Then, it was found that when **1a** was treated with 0.15 mM (15 mol%) of $Cu(NO_3)_2$ the reaction also proceeded to give 45% conversion of **1a** after 3 days, suggesting that the Cu^{II} ion is reduced *in situ* to the catalytically active Cu^{I} form (Table 1, entry 1).[39,40] Using a deoxygenated buffer and performing the reaction in a glove box to prevent back oxidation to Cu^{II} resulted in full conversion of **1a** to give 76% yield of **2a** (entry 2). Therefore, these conditions were selected for this study.

Self-assembly of the DNA-based catalyst was achieved by addition of a deoxygenated solution of commercially available salmon testes DNA (st-DNA) to a Cu^{II} complex in deoxygenated buffer. The formation of the cyclopropanation product was not obtained with $Cu(NO_3)_2$ alone in the presence of st-DNA (entry 3). Copper complexes of ligands **L1** and **L2** (Fig. 1) in combination with st-DNA, which afforded the highest ee values in the DNA-based catalytic reactions reported previously,[7,10–12] gave rise to a moderate conversion of **1a**, but no significant amount of cyclopropanation product was formed (entries 4 and 5). Using catalysts based on ligands **L3–L5a** that have a larger aromatic area, the cyclopropanation product **2a** was obtained in a yield of up to 19% (entry 8). Using 2 mM sodium ascorbate to enhance the rate of reduction to Cu^{I} did indeed result in a higher conversion of **1a**, but a lower yield of **2a** was obtained (entry 9).

These observations suggest the presence of a competing side reaction, which was expected to be the insertion reaction into the O–H bond of water,[41] a common reaction of metal–carbene complexes in aqueous solutions.[42–44] However, in the course of our study, the OH-bond insertion product **3a** was not detected in significant amounts in the crude product. Zwanenburg and

Table 1 Cu/DNA-catalysed intramolecular cyclopropanation of **1a**[a]

Entry	$Cu(NO_3)_2$ (mol%)	Ligand	Ligand (mol%)	Conversion[b] [%]	Yield[b] [%]	ee[b] [%]
Ligand to copper ratio 1 : 1[c]						
1[e]	15	—	—	45	17	0
2[f]	15	—	—	Full	76	0
3	15	—	—	38	0	0
4[g]	15	**L1**	15	42	0	0
5	15	**L2**	15	45	0	0
6	15	**L3a**	15	48	5	10
7	15	**L4**	15	63	10	28
8	15	**L5a**	15	73	19	37
9[h]	15	**L5a**	15	82	11	29
10	30	**L5a**	30	64	20	59
11[f]	15	**L5a**	15	Full	76	0
12	15	**L5b**	15	35	17	26
13	15	**L5c**	15	56	<5	<5
14	15	**L5d**	15	83	17	12
15	15	**L5e**	15	60	13	60
16	30	**L5e**	30	81	26	73
17[g]	15	**L6**	15	41	<5	<5
Ligand to copper ratio 2 : 1[d]						
18[i]	30	**L5a/L2**	30/30	80	20	61
19[i]	30	**L5a/L3b**	30/30	Full	28	76
20[g]	30	**L5a**	60	62	19	67
21[g]	30	**L5e**	60	62	30	84
22[g,j]	30	**L5e**	60	Full	46	83

[a] The experiments were carried out in a glove box, with 1 mM **1a**, 1.5 mM base pairs of st-DNA and the indicated concentration of Cu-complex in deoxygenated 10 mM MOPS buffer (pH 6.5), 2% v/v DMF, for 3 days at room temperature, unless otherwise specified. [b] Conversions, yields and enantioselectivities are based on areas of HPLC peaks that are compared to methyl phenyl sulfone as an external standard. All data were averaged over two experiments. Product **2a** was obtained in (1*R*,5*R*)-configuration by comparison of the elution order with those reported previously.[38] [c] Reproducibility: ee values and yields ±5%, conversions ±10%. [d] Reproducibility: ee values ±3%, yields ±5%, conversions ±10%. [e] Non-deoxygenated solution without DNA. [f] Without DNA. [g] Complex pre-formed in DMF prior to the reaction. [h] With 2 mM sodium ascorbate. [i] 30 mol% (0.30 mM) of isolated Cu-**L5a**, 0.30 mM of ligand **L2** or **L3b** added after incubation of Cu-**L5a** complex with st-DNA for 3 h. [j] 6 days reaction time.

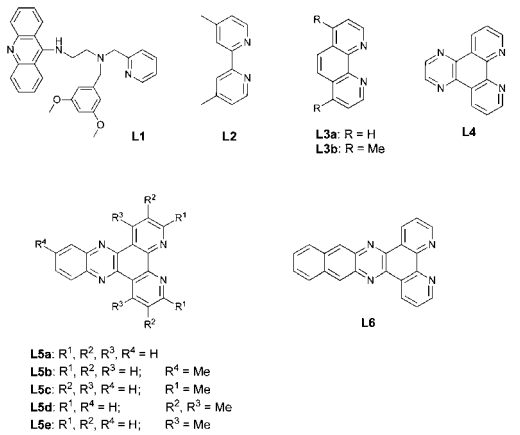


Fig. 1 Ligands used in this study.

Engberts reported that α-hydroxy sulfones,[45] which in this case are the products of O–H insertion, are rapidly decomposed in water, yielding the aldehyde **4a** and phenyl sulfinic acid **5** (Scheme 2).[46]

This hypothesis was tested by treating the model substrate **1b**, which cannot undergo cyclopropanation, with Cu-**L5a** in water. The ^{1}H-NMR spectrum of the lyophilized aqueous phase of the catalytic reaction showed only aromatic peaks corresponding to signals expected for phenyl sulfinic acid **5** or phenyl sulfonic acid, which would be the product resulting from oxidation of **5**. Additional mass analysis of the organic phase showed, among others, peaks at $m/z = 115$ and 141, indicating the presence of **4b** and **5** (see ESI† for spectra). These results strongly suggest the O–H insertion reaction with water, leading to the formation of **3a**, is the main side reaction occurring during the catalysis.

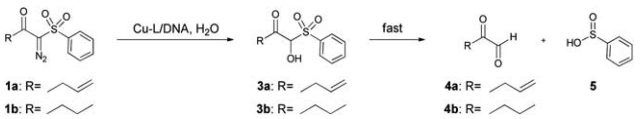
Interestingly, with st-DNA and the copper complex of ligand **L3a** enantioselectivity was observed for the first time (entry 6). The ee was found to increase when the aromatic system of the ligand became larger: up to 37% ee of the (1*R*,5*R*) enantiomer[38] was reached for product **2a** using dipyrido[3,2-*a*:2′,3′-*c*]phenazine (dppz, **L5a**), which is a known intercalator for DNA (entry 8).[47,48] Addition of 2 mM of sodium ascorbate, which gave rise to an increase in conversion but a decrease in yield (*vide supra*), also gave rise to a lower ee of **2a** (entry 9). Surprisingly, with the copper complex of ligand **L6** bearing an additional phenyl ring no product formation was observed (entry 17).

In the light of these results, the dppz ligand was used as the starting point for further optimization. Based on our previous experience that showed the beneficial effect of methyl substituents on bipyridine-type ligands in catalysis,[7,11] ligands **L5b–e** carrying methyl substituents at various positions on the dppz core were synthesized[49–51] and evaluated in the catalytic cyclopropanation. Using ligands **L5b** and **L5d**, **2a** was obtained in similar yields but with lower ee values, whereas with **L5c** no cyclization product was formed (entries 12–14). Surprisingly, with **L5e** that contains two methyl substituents located *para* to the nitrogens of the pyridine rings, the ee improved markedly to 60% (entry 15).

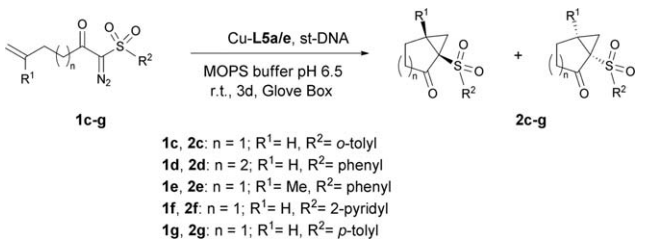
Addition of a second equivalent of ligand **L5a** to Cu-**L5a**-DNA led to a small increase in the ee (entry 20). Since it has been observed before that sometimes hetero-combinations of ligands can give rise to higher ee values in asymmetric catalysis,[52–54] also combinations of **L2** and **L3b** with pre-incubated Cu-**L5a**-DNA were evaluated. Indeed, it was observed that the enantioselectivity was increased to 76% in the case of **L3b** (entry 19). However, the best enantioselectivity, that is 84%, was obtained using two equivalents of ligand **L5e** with respect to copper (entry 21). This value represents the highest enantiomeric excess reported for product **2a** to date.

The substrate scope of the DNA-hybrid catalyzed asymmetric cyclopropanation was evaluated with a variety of different α-diazo sulfones **1c–g** (Scheme 3). With substrates **1c** and **1d** conversion was observed, but no cyclopropanation product was obtained (Table 2, entries 1 and 2). Apparently, the formation of the five membered ring **2c** with an *o*-tolyl group next to the sulfone and the formation of the six membered ring product **2d** were too slow and could not compete with the O–H bond insertion reaction. Substrate **1e** containing a methyl substituent at the internal position of the double bond also did not react under standard catalysis conditions (Table 2, entry 3). However, in contrast to **1c** and **1d**, addition of sodium ascorbate as a reducing agent to force the formation of the Cu^I species did result in cyclopropanation of **1e** giving 40% yield of **2e**, although the enantioselectivity was relatively low (Table 2, entry 4). In the cases of substrates **1f** and **1g** low yields of the cyclopropanation products were obtained and the observed enantioselectivities were moderate (Table 2, entries 5 and 6).

From the results above, a few notable observations can be made with regard to catalyst design and in particular the choice of the ligand for copper. First of all, a strongly intercalating ligand such as dppz or its derivatives is necessary in the DNA-based catalytic reaction to achieve formation of the cyclopropanation product. Most likely the dppz-based catalyst accelerates the cyclopropanation to such an extent that it can



Scheme 2 O–H bond insertion with Cu-L/DNA in water and subsequent decomposition. For **1b**: catalytic reaction with 1 mM **1b** and 0.15 mM Cu-**L5a** in water.



Scheme 3 Substrate investigation of Cu/DNA catalysed asymmetric cyclopropanation.

Table 2 Results of the substrate investigation[a]

Entry	Substrate	Conversion[b] [%]	Yield[b] [%]	ee[b] [%]
1	**1c**	78	0	n.d.
2	**1d**	26	0	n.d.
3[c]	**1e**	n.d.	2	n.d.
4[c,d]	**1e**	n.d.	40	16
5[c]	**1f**	n.d.	13	51
6[c]	**1g**	n.d.	29	63 (1*R*,5*R*)

[a] The experiments were carried out in a glove box, with 1 mM **1a**, 1.5 mM base pairs of st-DNA, 30 mol% (0.30 mM) of $Cu(NO_3)_2$ and 0.30 mM of **L5a** mixed in DMF prior to the reaction, in 10 mM of deoxygenated MOPS buffer (pH 6.5), 2% v/v DMF, for 3 days at room temperature, unless otherwise specified. n.d. = not determined. [b] Conversions, yields and enantioselectivities are based on areas of HPLC peaks that are compared to methyl phenyl sulfone as external standard. All data are averaged over two experiments. Reproducibility: ee values and yields ±5%, conversions ±10%. [c] 30 mol% (0.30 mM) of $Cu(NO_3)_2$ and 0.60 mM of **L5e** mixed in DMF prior to the reaction. [d] With 2 mM sodium ascorbate.

compete with the O–H bond insertion reaction. Additionally, dppz derivatives were also the ligands with which the highest ee values were achieved in the catalyzed reaction. These observations are in marked contrast with the previously reported DNA-based Cu^{II} catalyzed C–C bond forming reactions in which the complexes of weakly binding ligands that are not pure intercalators, such as bipyridines, always gave rise to higher activities and selectivities. A tentative explanation for this observed difference is that in the present case, the kinetically stable and structurally rigid stacking of the intercalating ligands of the copper complex between the base-pairs of the DNA results in a microenvironment that limits access of surrounding water to the catalytic site, *i.e.* the Cu^{I}–carbene complex. Thus cyclopropanation is favored compared to O–H insertion. Moreover, the close proximity of the catalyzed reaction to the chiral DNA helix results in an efficient transfer of chirality and, as a result, high enantioselectivity in the product.

Secondly, in line with previous observations, it was found that methyl substituents on selected positions of the ligand resulted in higher enantioselectivities in the catalyzed reaction. Strikingly, the relative positions of these methyl substituents are the same as in ligand **L2**, which similarly gave significantly higher ee values compared to unsubstituted 2,2′-bipyridine in DNA-based Lewis acid catalyzed reactions.[55] The reason for the importance of methyl groups at these positions, which are remote from where the catalysis occurs is intriguing but at present not understood. Finally, the highest ee values were obtained using ligand to copper ratios of 2 : 1. No, or only a negligible increase of enantioselectivity was reported before for Cu^{I} catalyzed insertion reactions with ligand to copper ratios of 2 : 1.[56,57]

Conclusions

Here, we have shown the first examples of DNA-based asymmetric organometallic catalysis in water resulting in high ee values. Up to 84% ee was achieved in the intramolecular cyclopropanation of α-diazo-β-keto sulfones. Additionally, this study represents, to the best of our knowledge, the first copper catalyzed asymmetric cyclopropanation in water.[58] Even though O–H bond insertion is a major side reaction for copper–carbenes in water, these results do demonstrate for the first time that enantioselective organometallic catalysis is feasible using the DNA-based asymmetric catalysis concept. Thus, this study unequivocally demonstrates that DNA-based catalysis can be expanded beyond Lewis acid catalyzed reactions and provides a promising basis for further explorations of DNA–metal-hybrid catalysts for synthetically important transformations in water.

Acknowledgements

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